REMARKS

Claims 1-23 and 48-84 are pending in this application. Claims 24-47 have been withdrawn from further consideration as being drawn to nonelected subject matter. Claims 1-23 and 48-84 were provisionally rejected as allegedly being unpatentable under the judicially created doctrine of obviousness-type double patenting. Claims 1-21, 48-67, 70-78 and 81-84 were rejected under 35 U.S.C. §112, first paragraph. Claims 1-23 and 48-84 were rejected under 35 U.S.C. §112, second paragraph. Claims 1 -23 and 48-84 were variously rejected under 35 U.S.C. §102(b). Claims 1 -23 and 48-84 were variously rejected under 35 U.S.C. §102(e).

By this amendment, claims 1, 48 and 70 have been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification. Support for the amendments to claims 1, 48 and 70 is found, *inter alia*, at page 31, line 11, page 42, lines 9-11 and page 63, lines 19-25.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Specification Objection

The specification was objected to for containing an embedded hyperlink and/or other form of browser-executable code at page 41. The specification has herein been amended to delete the hyperlink. Applicants respectfully request withdrawal of this objection.

Rejections Under Obviousness-Type Double Patenting

Claims 1-23 and 48-84 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-15, 18-22, 27-29 and 51-62 of copending Application No. 10/214,799.

Applicants thank the Examiner for bringing the co-pending application to Applicants' attention. Since this is a provisional obviousness-type double patenting rejection and there are no issued claims, there is nothing to disclaim at this time. Thus, this rejection is moot.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-21, 48-67, 70-78 and 81-84 were rejected under 35 U.S.C. §112, first paragraph, for allegedly claiming subject matter which was not described in the specification in such a way as to enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

The Examiner states that the "specification contemplates that the claimed invention would be used as a pharmaceutical or therapeutic composition for in vivo use" and that "[a polynucleotide] would require a phosphorothioate backbone to avoid degradation of the motif when administered to an individual." Office Action, page 4. A review article by Plenat[1] regarding use of antisense oligonucleotides *in vivo* was cited in support this position.

[1] Plenat (1996) "Animal models of antisense oligonucleotides: lessons for use in humans," *Molecular Medicine Today* 1:250-257.

Applicants respectfully point out that the claimed invention is directed to a complexes comprising the polynucleotide (IMP) linked to the surface of a biodegradable microcarrier (MC) and that the specification describes administration of the claimed complexes to an individual. Unlike the that described in Plenat, the polynucleotides of the invention are administered in the context of the IMP/MC complex. Plenat provides no evidence that the degradation behavior of polynucleotides attached to the surface of a MC is the same as that of polynucleotides free in solution. Thus, the discussion of Plenat regarding administration of antisense oligonucleotides, for example at page 250, is not directly applicable to the claimed invention and does not support the enablement rejection of the claimed invention.

Further, Applicants have provided herein, in the form of a Declaration from Dr. Van Nest, experimental results which demonstrate that IMP/MC complexes comprising a phosphodiester polynucleotide are as effective as IMP/MC complexes comprising a phosphorothioate polynucleotide in immunomodulatory activity assays. Dr. Van Nest's Declaration provides results of immunostimulatory assays with human PBMCs as described in the specification.

Dr. Van Nest's Declaration provides results of experiments performed with phosphodiester and phosphorothioate polynucleotides in solution and in an IMP/MC complex. The experiments were performed and the complexes were prepared as described in the specification. The experimental data presented therein demonstrates that the IMP/MC complex made with the phosphodiester polynucleotide was active in inducing both IFN-α and IFN-γ despite the phosphodiester polynucleotide being inactive when used alone. The data demonstrates that polynucleotides containing either phosphorothioate or phosphodiester linkages in MC complexes are effective in stimulating IFN production from human PBMCs.

Thus, Applicants respectfully submit that contrary to the Examiner's assertion, a phosphorothioate backbone is not required for the polynucleotides in the claimed complexes and the pending claims are in compliance with the enablement requirement.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1-23 and 48-84 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

Applicants have attempted to respond to the concerns of the Examiner in order to enhance clarity and to facilitate disposition of the present case.

The Examiner states that the "claims are vague and indefinite in the recitation of "5'-C,G-3'"; what does Applicants intend?" Office Action, page 4.

Applicants respectfully point out that, as commonly known in the art, the conventional way to indicate the particular arrangement of contiguous nucleotides in a nucleic acid molecule is to bracket the specific nucleotide sequence with a " 5' " and a " 3'." The 5' is used to indicate the free 5' hydroxyl or phosphate at one end of the nucleic acid molecule and the 3' is used to indicate the free 3' hydroxyl group at another end of the nucleic acid molecule. Thus, the phrase "the sequence 5'-C,G-3" of the claims indicates that the claimed polynucleotide contains a sequence with a contiguous cytosine, guanosine in a 5' to 3' orientation relative to each other. Accordingly, Applicants respectfully submit that the phrase "sequence 5'-C,G-3'" does not render the claimed invention indefinite and that the claims are sufficiently definite when considered in view of the specification and the understanding of those of skill in the art.

The Examiner states that claim 13 "lacks positive antecedent basis in the recitation of "5'-TCGTCGX$_1$-3'"; this is not one of the sequences of claim 12." Office Action, page 5. Applicants respectfully point out that claim 12 recites the sequence "5'-TCGX$_1$X$_2$X$_3$X$_4$-3'"

"wherein X_1, X_2, X_3, X_4 are nucleotides." Claim 13 is directed to the claim 12 sequence where $X_1X_2X_3$ are TCG and the remaining X is a nucleotide.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. §102

35 U.S.C. § 102(b)

Claims 1-23 and 48-84 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Carson *et al.* (WO 98/16247, "Carson"), WO 99/11275 or Schwartz *et al.* (WO 98/55495, "Schwartz"). Applicants respectfully traverse this rejection.

The claimed invention is directed to a complexes comprising a 5'-C,G-3'-containing polynucleotide (IMP) linked to a biodegradable microcarrier (MC). As described on page 42, lines 9-11, of the specification, "IMP/MC complexes comprise an IMP bound to the surface of, or inserted into, a microcarrier (i.e., the IMP is not encapsulated in the MC)." Accordingly, the claims have herein been amended to more clearly indicate that the IMP is linked to the surface of the microcarrier.

For a claim to be anticipated by a reference, the reference much teach each and every element of the claim. As discussed below, neither of the cited references teach 5'-C,G-3'-containing polynucleotides linked to the surface of a biodegradable microcarrier, *i.e.*, not encapsulated in the microcarrier. Accordingly, Applicants respectfully submit that the references do not anticipate the claimed invention.

Schwartz

Schwartz describes co-administration of an immunostimulatory polynucleotide (ISS), antigen and adjuvant, where the adjuvant includes emulsions, alum, liposomes and microparticles.

Schwartz also describes compositions comprising an ISS, an immunomodulatory molecule and an encapsulating agent in the form of emulsions, microparticles and/or liposomes and "adjuvant oil-in-water emulsions, microparticles and/or liposomes encapsulating an ISS-immunomodulatory molecule in the form of particles."[2]

Although Schwartz describes mixtures of ISS with antigen and adjuvant, including microcarriers, Schwartz does not describe a complex in which an IMP is linked to the surface of a microcarrier.

Since Schwartz does not teach each and every element of the claimed invention, Schwartz does not anticipate the claimed invention.

Carson

Carson describes administration of an immunostimulatory polynucleotide conjugated to an antigen. Carson mentions that a colloidal dispersion system may be used to administer the immunostimulatory polynucleotide,[3] however, Carson does not describe a complex in which an IMP is linked to the surface of a microcarrier, much less a complex in which an IMP is linked to the surface of a biodegradable microcarrier.

Since Carson does not teach each and every element of the claimed invention, Carson does not anticipate the claimed invention.

WO 99/11275

WO 99/11275 describes administration of an immunostimulatory polynucleotide without co-delivery of an immunizing antigen. WO 99/11275 mentions that a colloidal dispersion system may be used to administer the immunostimulatory polynucleotide,[4] however, WO 99/11275 does not describe a complex in which an IMP is linked to the surface of a microcarrier, much less a complex in which an IMP is linked to the surface of a biodegradable microcarrier.

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[2] See, for example, Schwartz, page 15, lines 10-18, and page 15, line 38, to page 16, line 2.
[3] See, for example, Carson at page 31, lines 5-9.
[4] See, for example, WO 99/11275 at page 19, lines 1-4.

Since WO 99/11275 does not teach each and every element of the claimed invention, WO 99/11275 does not anticipate the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b).

35 U.S.C. § 102(e)

Claims 1-23 and 48-84 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Raz *et al.* (U.S. Pat. No. 6,534,062, "Raz") or Friede *et al.* (U.S. Pat. No. 6,544,518, "Friede"). Applicants respectfully traverse this rejection.

As an initial matter, Applicants respectfully point out that the present invention claims priority to the provisional patent application number 60/188,303, filed March 10, 2000. The earliest application Raz claims priority to is a provisional application filed March 28, 2000. Thus, Raz is not a properly cited reference under 35 U.S.C. §102(e). Accordingly, Applicants respectfully request withdrawal of the rejection based on Raz.

Secondly, Friede does not describe a complex in which an IMP is linked to the surface of a microcarrier, much less a complex in which an IMP is linked to the surface of a biodegradable microcarrier.

For a claim to be anticipated by a reference, the reference much teach each and every element of the claim. Thus, Friede does not teach the claimed invention. Accordingly, Applicants respectfully submit that Friede does not anticipate the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102(e).

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001420.

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Respectfully submitted,

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